REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-28 are pending in the application. Claims 24-28 stand withdrawn from consideration. Claims 1-23 have been rejected. Accordingly, claims 1-23 remain under consideration.

Rejections Under 35 USC § 103(a)

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamatatos and Cheng-Mayer (1998). This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The Stamatatos et al. reference as a whole. The Stamatatos et al. reference is an article that demonstrates that deletion of the V2 loop from a clade B HIV-1 isolate results in neutralization of the virus by sera derived from patients infected with clade A, B, C, D, E and F HIV-1 isolates. While the authors propose that the use of the envelope from the virus having the V2 region deletion could be used to generate antibodies against the exposed region, no data is provided to support this theory. In particular, Stamatatos et al. **do not prepare antibodies against the envelope proteins derived from the V2 deletion isolate, nor do they provide evidence that antibodies prepared against the envelope proteins from this V2 isolate exhibit broad neutralization properties.** Furthermore, Stamatatos et al. **do not demonstrate that antibodies raised against the envelope proteins from this V2 deletion isolate are protective antibodies.**

The analysis under § 103(a). Stamatatos et al do not teach that the clade B isolate having the V2 loop deleted can elicit a broad heterologous humoral immune response including the generation of neutralizing and protective antibodies when administered to animals, as presently claimed in the instant application. Demonstrating neutralization of certain viral isolates, such as the clade B isolate claimed herein, with sera taken from patient samples **does not suggest** that the same viral isolate, when injected into animals, will elicit a broad heterologous antibody response. Applicants assert that the Stamatatos et al reference merely demonstrates that the V2 loop deletion makes the virus more susceptible to serum mediated neutralization, which is not the same as demonstrating that the virus containing the V2 loop deletion is capable of eliciting a broad and heterologous antibody response in vivo. In fact, several lines of evidence suggest that the opposite is true, that is, certain investigators teach away from the concept proposed. In support of this, Applicant(s) have submitted four articles in a Supplemental Information Disclosure Statement on March 8, 2004 as evidence that induction of a heterologous antibody response using techniques to enhance the immunogenicity of viral envelope proteins by a mutation or modification in the V1, V2 or V3 loop of HIV-1 isolates does not necessarily result in such an outcome under carefully controlled experimental conditions. In fact, several of these investigators demonstrated that while the viral envelope proteins having deletions in the loop domains were able to induce an antibody response as demonstrated by an enzyme-linked immunosorbent assay (ELISA), these antibodies were not able to neutralize heterologous virus strains. Thus, these studies teach away from the Stamatatos et al. reference. That is, while the viral isolates having the various loop deletions or mutations appeared to be more immunogenic, as shown by ELISA assays, **removal or modification of these loop domains did not improve the ability of the envelope proteins to raise neutralizing antibodies**. The Applicant(s) provide herein a copy of these references for the Examiner's convenience as Exhibit A as corroboration of the level of knowledge to one skilled in the art at the time the invention was made.

For example, Haigwood et al., (1990), (AIDS Research and Human Retroviruses, Vol. 6, No. 7: 855-869), created variants of the HIV-1 env gene whereby one or more of the hypervariable domains of gp120 were deleted. The purified antigens were then used to immunize animals to determine if they could elicit neutralizing antibodies. Furthermore, they tested the specificity of the neutralizing antibodies elicited. Their results demonstrated that while each

variant generated an antibody response as measured by enzyme-linked immunosorbent assay (ELISA), heterologous neutralizing antibodies could not be generated. The Examiner's attention is directed to page 864, first paragraph, whereby the investigators note the following:

> *"Finally, when antisera to env 2-3 D(1-5), the variant from which all five hypervariable regions were deleted, was tested, no HIV-SF2 neutralizing antibodies were detected, even though this protein was highly immunogenic (see ELISA data)."*

Similarly, Bolmstedt et al, (1996), (Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 12: 213-220), performed site-directed mutagenesis to generate a gp160 which was depleted of three N-linked glycans in the CD4-binding domain to determine whether in so doing, they could generate a broadly neutralizing antibody response. While both the wild type and mutant envelope gp160 elicited an antibody response as measured by an enzyme linked immunosorbent assay (ELISA), the antibodies generated did not neutralize non-related HIV strains. The Examiner's attention is drawn to the last sentence of the Summary on page 213 of the enclosed article:

> *"These data indicated that elimination of the three N-linked glycans from gp160 resulted in an altered local antigenic conformation but did not uncover hidden neutralization epitopes, broadening the immune response."*

Furthermore, Kim et al (2003), (Virology, 305:124-137), attempted to elicit a broad heterologous antibody response to HIV-1 using various loop deleted envelope proteins expressed recombinantly in vaccinia virus. Once again, although all of the envelope constructs elicited similar levels of gp120-binding antibodies when analyzed by enzyme-linked immunosorbent assay (ELISA), only the wild type demonstrated the highest level of neutralizing antibody activity against the same, but not against different isolates. Thus, their results suggest that obtaining broadly reactive neutralizing antibodies may not be achieved by deleting the variable loops of gp120, including the V2 loop. The Examiner's attention is drawn to the last paragraph on page 133, whereby the authors state:

"Our results clearly indicate that obtaining broadly reactive Nabs might not be achieved by simply deleting the variable loops of gp120."

And finally, Lu et al. (1998), (AIDS Research and Human Retroviruses, Vol. 14, No. 2: 151-155), attempted to generate heterologous antibodies using DNA vaccines that expressed the HIV-1 envelope glycoproteins with or without deletions in the variable regions V1/V2 and V3. Their results demonstrated that while removing the V1/2 and V3 variable regions increased the immunogenicity as shown by enzyme linked immunosorbent assay (ELISA), they did not improve the ability of the envelope glycoproteins to raise neutralizing antibodies. The Examiner's attention is drawn to the third paragraph on page 155, whereby the authors state:

"Disappointingly, although deletion of the variable regions increased the titers of ELISA antibody raised by the gp140 and gp160 forms of Env, these structural changes ***reduced*** *the ability of Env-expressing DNAs to raise neutralizing antibody (Table 2)."*

Applicant(s) respectfully request withdrawal of the Examiner's rejection for the following reasons. According to the Examiner's assessment, the Stamatatos et al. reference provides a suggestion to the skilled artisan that the viral envelope having the V2 region deleted would be a target to consider for immunization purposes. However, there is no evidence in the Stamatatos et al. reference or the extant art, as provided herein, to confirm that such a method would work. As the Examiner will appreciate, the "obvious to try" rationale is insufficient to establish that the skilled artisan was given the required suggestion by the cited reference to arrive at the present invention so that the invention is thereby rendered obvious. There must be objective evidence that the proposed method would work. There is no objective evidence in the cited Stamatatos et al. reference that leads one skilled in the art to conclude that the methods of the present invention for elicitation of a broad heterologous antibody response would work, and thus would not motivate the skilled artisan to arrive at the present invention. Only through the Applicant(s) work included in the instant application has the evidence been provided.

Furthermore, obviousness requires a reasonable expectation of success. Applicant(s) respectfully assert that as related to the claims as filed, a reasonable expectation for success would be questionable based on the level of skill in the art at the time that the present invention was made. Several investigators tried various means of altering the variable loop domains of HIV-1 in order to generate antibodies with broad heterologous neutralization capability, but have failed. It was not until the time of the present invention that a broad heterologous antibody response was demonstrated using the HIV-1 construct having the V2 loop deletion as claimed. It is only through the findings in the present application that success was attained.

Furthermore, it should be noted that development of the subject matter of the present invention did not follow immediately after the speculation referred to in the publication of Stamatatos et al. In fact, more than two years passed before the present Applicant(s) were able to demonstrate success in development of the strategy and materials disclosed in the present application. Accordingly, if the present invention were obvious in light of the Stamatatos et al. reference, one might speculate that success of the purported strategy should have ensued much sooner than the present invention, which was not the case.

Accordingly, Applicants respectfully request withdrawal of the rejection.

Fees

A check in the amount of $420 for a two-month extension of time is enclosed. No other fees are believed to be required, but if so, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the arguments provided herein put the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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Enclosures: Petition for Two Month Extension of Time
Exhibit A (Four references previously forwarded in a Supplemental IDS)